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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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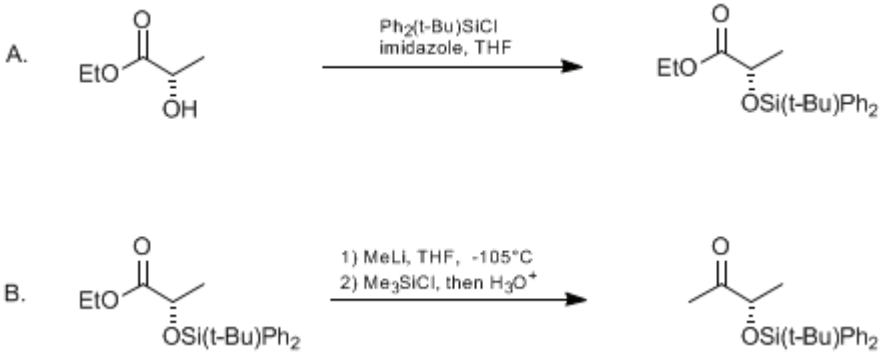
3-(S)-[(tert-BUTYLDIPHENYLSILYL)OXY]-2-BUTANONE

[2-Butanone, 3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-, (S)-]



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1. Procedure

A. *Ethyl 2-(S)-[(tert-butyldiphenylsilyl)oxy]propanoate.* An oven-dried, 500-mL, round-bottomed flask is equipped with a magnetic stirring bar and purged with dry argon. The flask is charged with 10.0 g (84.6 mmol) of (S)-(−)-ethyl lactate, 23.3 g (84.6 mmol) of tert-butyldiphenylsilyl chloride, 14.4 g (211 mmol) of imidazole, and 50 mL of dry tetrahydrofuran (Note 1). The resulting white suspension is stirred vigorously at 23°C for 2 hr. (At the beginning of the stirring, a heated water bath is useful to maintain the reaction temperature.) The mixture is then filtered through glass wool into 400 mL of water and the solids are washed with two 25-mL portions of tetrahydrofuran. The filtrate is concentrated to remove tetrahydrofuran under reduced pressure using a rotary evaporator. The resulting aqueous suspension is transferred to a 1-L separatory funnel and is extracted with 400 mL of ethyl acetate. The organic phase is washed with two 400-mL portions of water, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure using a rotary evaporator to give 30.0 g (99%) of ethyl 2-(S)-[(tert-butyldiphenylsilyl)oxy]propanoate as a clear colorless oil (Note 2).

B. *3-(S)-[(tert-Butyldiphenylsilyl)oxy]-2-butanone.* An oven-dried, 1-L, three-necked, round-bottomed flask is charged with 20.0 g (56.2 mmol) of ethyl 2-(S)-[(tert-butyldiphenylsilyl)oxy] propanoate and the flask is fitted with a mechanical stirrer, a 100-mL addition funnel, and a rubber septum. A low temperature thermometer (Note 3) is inserted through the rubber septum and 250 mL of dry tetrahydrofuran (Note 1) is injected with a syringe. The mechanically stirred solution is cooled to −105°C (Note 4) and maintained until the temperature has stabilized. The addition funnel is charged with 52 mL of a 1.4 M ether solution of halide-free methyllithium (73 mmol) and this solution is added dropwise with mechanical stirring over 35–40 min. The internal temperature is never allowed to rise above −100°C (Note 5). When addition is complete, 20 mL (158 mmol) of trimethylsilyl chloride (Note 6) is injected and the resulting clear solution is warmed to room temperature over 20 min with the aid of a water bath. At this time 200 mL of 1 N hydrochloric acid is added and vigorous stirring is continued for 1 hr (Note 7). The mixture is poured slowly into a 2-L Erlenmeyer flask containing 30 g of solid sodium bicarbonate and then concentrated to remove tetrahydrofuran under reduced pressure using a rotary evaporator. The resulting aqueous suspension is transferred to a 1-L separatory funnel and extracted with 400 mL of ethyl acetate. The organic layer is washed with two 400-mL portions of water, dried over anhydrous sodium sulfate, filtered, and concentrated using a rotary evaporator to give 18.2 g (99%) of 3-(S)-[(tert-butyldiphenylsilyl)oxy]-2-butanone as a clear colorless oil (Note 8) and (Note 9).

2. Notes

1. (S)-Ethyl lactate, $[\alpha]_D^{14}$ −10° (neat) and other chemicals employed in this procedure were obtained

from Aldrich Chemical Company, Inc. Anhydrous tetrahydrofuran was prepared by distillation under argon from sodium benzophenone ketyl.
2. Gas chromatographic analysis using a 25-m 10% SP 2100 silicone column showed that this sample was >95% pure and contained one major unidentified impurity. Material of this purity is acceptable for use in the second step. A sample showing no detectable impurities by GLC analysis can be obtained by flash chromatography on silica gel (5:95 ethyl acetate-hexane). This sample has the following spectral characteristics: $[\alpha]_D$ −45.1° (MeOH, *c* 1.0); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.09 (s, 9 H, t-Bu), 1.14 (t, 3 H, J = 7.1, OCH_2CH_3), 1.37 (d, 3 H, J = 6.7, CH_3), 3.99–4.04 (m, 2 H, OCH_2CH_3), 4.27 (q, 1 H, J = 6.7, CH), 7.36–7.41 (m, 6 H, Ph), 7.65–7.69 (m, 4 H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.0, 19.2, 21.2, 26.8, 60.5, 68.9, 127.6, 129.7, 133.1, 133.5, 135.7, 135.8, 173.6; IR (film) cm^{-1}: 2980, 2933, 2859, 1753, 1735, 1429, 1198, 1139, 1112, 1081, 823, 739, 702, 690, 611. Anal. Calcd for $C_{21}H_{28}O_3Si$: C, 70.74; H, 7.92. Found: C, 70.94; H, 7.89.
3. An OMEGA 450 ATT (Type T) thermocouple thermometer was used.
4. A minimum amount of liquid nitrogen contained in a 1-L Dewar bowl was used to cool the solution to −105°C.
5. It is crucial that the internal temperature of the reaction mixture never exceed −100°C during the addition of the methyllithium solution. If the temperature begins to rise, the dropwise addition of the reagent should be slowed. Periodic addition of a small amount of liquid nitrogen to the cooling bath may also be necessary.
6. Trimethylsilyl chloride is distilled from calcium hydride and stored under argon or nitrogen in a stoppered bottle over polyvinylpyridine.
7. Hydrolysis of the reaction mixture may be accomplished by addition of 200 mL of water instead of 200 mL of 1 N hydrochloric acid. In the former case complete hydrolysis requires 5 hr and in the latter hydrolysis is complete within 1 hr.
8. Gas chromatographic analysis using a 25-m 10% SP 2100 silicone column showed that this sample was >95% pure and contained one major unidentified impurity. A sample of 100% purity may be obtained by flash chromatography on silica gel (1:9 ethyl acetate-hexane). This sample has the following spectral characteristics: $[\alpha]_D$ −3.1° (MeOH, *c* 1.0); ^{1}H NMR (300 MHz, $CDCl_3$): δ: 1.10 (s, 9 H, t-Bu), 1.19 (d, 3 H, J = 6.8, CH_3), 2.16 (s, 3 H, $COCH_3$), 4.17 (q, 1 H, J = 6.8, CH), 7.36–7.40 (m, 6 H, Ph), 7.60–7.66 (m, 4 H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.2, 20.6, 24.9, 26.9, 75.7, 127.6, 127.8, 129.9, 135.7, 211.7; IR (film) cm^{-1}: 2961, 2933, 2859, 1719, 1428, 1114, 823, 741, 703, 691; MS (Cl) m/z 327.1760 (327.1780 calcd for $C_{20}H_{26}O_2Si$, MH). Anal. Calcd for $C_{20}H_{26}O_2Si$: C, 73.57; H, 8.03. Found: C, 73.52; H, 8.07.
9. The enantiomeric excess of the product is >96%. This was determined by treating a sample of the ketone sequentially with methyllithium and tetrabutylammonium fluoride (THF, −78°C). The resulting diol was converted to its Mosher diester[2,3] [2.5 eq of (+)-α-methoxytrifluoromethylphenylacetic acid, 3 eq of dicyclohexylcarbodiimide, and 0.2 eq of 4-(dimethylamino)pyridine, CH_2Cl_2] and the crude esterification reaction mixture was analyzed using 500 MHz ^{1}H NMR. None of the minor diastereomer was observed; doping experiments established that 2% of the minor diastereomer would have been detected [diagnostic signals: d 5.03 (q, J = 6.2, major diastereomer); δ 5.17 (q, J = 6.1, minor diasteromer)].

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The sequence detailed here provides 3-(S)-((tert-butyldiphenylsilyl)oxy)-2-butanone in high purity and on a preparative scale from inexpensive (S)-ethyl lactate. This optically active ketone should be a useful intermediate for the preparation of a variety of enantiomerically pure materials. It has been used in our laboratory for an asymmetric synthesis of (+)-muscarine[4] and in the preparation of various other optically active tetrahydrofurans.[5] Mitsunobu inversion of (S)-ethyl lactate followed by protection to provide 2-(R)-((tert-butyldiphenylsilyl)oxy)propanoate[6] affords, by this method, ready access to the enantiomer of the title compound.

Conversions of carboxylic acids to ketones are typically performed in stepwise fashion[7] via intermediates such as acid chlorides,[8 9 10 11] anhydrides,[12] thioesters,[13] or N-alkoxy amides,[14 15] or by the direct reaction of carboxylic acids with lithium reagents.[16] In this latter method trimethylsilyl chloride has been shown to be an effective reagent for trapping the tetrahedral alkoxide intermediates and for quenching excess organolithium reagent.

The addition of trimethylsilyl chloride proved crucial to the success of the procedure described here. Use of aqueous ammonium chloride as a quenching reagent (instead of trimethylsilyl chloride) resulted in a reaction mixture that contained up to 30% of the corresponding tertiary alcohol.

Preliminary investigations into the generality of this synthesis of lactate-derived ketones using other alkyl lithium reagents including butyllithium and phenyllithium have not been as successful. Product mixtures were typically contaminated with significant amounts of both the tertiary alcohol and the starting ester.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 4

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

sodium benzophenone ketyl

(+)-muscarine

(S)-(−)-ethyl lactate

polyvinylpyridine

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Phenyllithium (591-51-5)

lithium (7439-93-2)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

Imidazole (288-32-4)

Methyllithium (917-54-4)

argon (7440-37-1)

calcium hydride (7789-78-8)

dicyclohexylcarbodiimide (538-75-0)

trimethylsilyl chloride (75-77-4)

ethyl acetate-hexane (2639-63-6)

Tetrabutylammonium fluoride (429-41-4)

4-(dimethylamino)pyridine (1122-58-3)

(+)-α-methoxytrifluoromethylphenylacetic acid (56135-03-6)

tert-butyldiphenylsilyl chloride (58479-61-1)

3-(S)-[(tert-Butyldiphenylsilyl)oxy]-2-butanone,
3-(S)-((tert-butyldiphenylsilyl)oxy)-2-butanone,
2-Butanone, 3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-, (S)- (135367-18-9)

Ethyl 2-(S)-[(tert-butyldiphenylsilyl)oxy]propanoate (102732-44-5)

(S)-ethyl lactate (97-64-3)

2-(R)-((tert-butyldiphenylsilyl)oxy)propanoate